

# CONCEPT PAPER

## RISK MANAGEMENT PROGRAMS

*DRAFT*

*This concept paper is being distributed for comment purposes only.*

Submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852; e-mail [fdadockets@oc.fda.gov](mailto:fdadockets@oc.fda.gov); or on the internet at <http://www.accessdata.fda.gov/scripts/oc/dockets/edockethome.cfm>. Written or electronic comments on the concept papers will be accepted until April 30, 2003. All comments should be identified with docket number 02N-0528 and wherever possible, reference the comments to specific sections or line numbers of the document.

For questions on the content of this draft document contact Christine Bechtel, 301-594-5458.

March 3, 2003

## CONCEPT PAPER: RISK MANAGEMENT PROGRAMS

*If you plan to submit comments on this concept paper, to expedite FDA review of your comments, please:*

- *Clearly explain each issue/concern and, when appropriate, include an alternative proposal and the rationale and/or justification for employing the alternative.*
- *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*

### I. INTRODUCTION

In accordance with Section VIII of the PDUFA III Reauthorization Performance Goals and Procedures, the CDER/CBER Risk Management Working Group is drafting guidance for industry on the development, implementation, and evaluation of drug and biological product<sup>1</sup> risk management programs. This concept paper is intended to facilitate public discussion on the content of the draft guidance by outlining FDA's proposed approach and requesting comment. Specifically, this concept paper presents FDA's preliminary thoughts on:

- Considerations for initiating and designing a risk management program
- The selection and development of risk management tools
- The evaluation of risk management programs
- The recommended elements of a risk management program submission

### II. IMPORTANT RISK MANAGEMENT CONCEPTS

#### A. What is risk management?

FDA approval of a product means FDA believes that it is safe and effective for its labeled indications under its labeled conditions of use. FDA's determination that a product is safe, however, does not suggest an absence of risk. Rather, a product is considered to be safe if the clinical significance and probability of beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a product is considered safe if it has a positive benefit/risk balance on a population and individual patient level.

Risk management is the overall and continuing process of minimizing risks throughout a product's lifecycle to optimize its benefit/risk balance. Risk information emerges continuously throughout a product's lifecycle, during both the investigation and marketing phases through both labeled and off-label uses. FDA considers risk management to be a continuous process of (1) learning about and interpreting a product's

---

<sup>1</sup> For ease of reference, this concept paper uses the term *product* to refer to all products (excluding blood products other than plasma derivatives) regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). Similarly, for ease of reference, this concept paper uses the term *approval* to refer to both drug approval and biologic licensure.

benefits and risks, (2) designing and implementing interventions to minimize a product's risks, (3) evaluating interventions in light of new knowledge that is acquired over time, and (4) revising interventions when appropriate.

**B. What aspects of risk management are addressed in this concept paper?**

This concept paper defines and discusses risk management programs and submissions. Risk management programs are one result of the overall process of risk management planning, which also encompasses good risk assessment and pharmacovigilance. These latter two topics are covered in separate concept papers entitled: (1) *Premarketing Risk Assessment*, and (2) *Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.

**C. What is risk management planning?**

FDA proposes that the sponsor of every product submitted for approval consider how to minimize risks from the product's use. Risk management planning generally encompasses all efforts by a sponsor to minimize the risk from its product's use and may include product labeling, risk assessment, pharmacovigilance, and special studies or interventions. All products have some kind of risk management planning. For most products, traditional risk management planning consists of professional product labeling (i.e., the package insert or PI) and postmarketing surveillance. However, the PI alone is not always sufficient to minimize a product's risks. In these cases, FDA proposes that sponsors submit a risk management program (RMP) as defined below.

**D. What is a risk management program (RMP) and what are its goals and objectives?**

FDA is defining a risk management program (RMP) as a strategic safety program designed to decrease product risk by using one or more interventions or tools beyond the package insert.<sup>2</sup> Examples include (1) specialized educational materials for health care practitioners or patients, (2) processes or forms to increase compliance with reduced-risk prescribing and use, and (3) systems that modify conventional prescribing, dispensing, and use of the product to minimize specific risks.

An RMP could be considered similar to a clinical development program with one or more risk reduction (or safety) goals as its endpoint. We believe the best risk reduction goals would be tailored to the specific risk(s) of concern and, to the extent possible, evidence-based methods would be used to target the achievement of critical processes, behaviors, and human factors to increase safety. For example, if product safety can be increased by judicious patient selection for therapy, one goal might be appropriate prescribing and dispensing to the appropriate patient group. Another example would be if a product's risk

---

<sup>2</sup> The package insert (PI) is that portion of approved product labeling described in 21 CFR 201.57 that is directed primarily to health professionals. The PI should not be confused with approved product labeling which may incorporate RMP materials such as Medication Guides and patient agreements in addition to the PI.

increases due to patient factors such as misuse or poor self-monitoring; in this case, a goal of adequate patient education regarding product use could be established.

Much like a clinical development program's goals are translated into individual protocols each designed to measure achievement of a particular outcome, RMP goals would be translated into pragmatic, specific and measurable program objectives that result in processes or behaviors leading to RMP goals being achieved. Objectives can be thought of as intermediate steps to achieving the overall RMP goal. An RMP goal could be translated into a variety of objectives depending upon the type and severity of the specific risks being managed. For example, an RMP goal could specify that no patient with condition A will be given product B. Illustrative examples of objectives for achieving such a goal could include one or more of the following:

1. Physicians will be fully knowledgeable about the need to withhold product B from patients with condition A
2. Candidate patients for product B will be fully knowledgeable that condition A is a reason not to take product B, and will know how to (1) inform their prescriber, or (2) help their prescriber detect if they have condition A
3. Pharmacists will confirm that patients with a product B prescription do not have condition A.

### **III. WHEN WOULD AN RMP BEYOND THE PACKAGE INSERT BE APPROPRIATE?**

Since risk characterization (through identification and evaluation) is an ongoing process throughout a product's lifecycle, a perceived need for an RMP may emerge pre- or post-approval. Ideally, an RMP would be developed, submitted, and modified as risk reduction needs are identified in a product's lifecycle.

At any point in product development or approval, a sponsor could voluntarily submit a proposed RMP for Agency review and comment. Alternatively, FDA may propose to the sponsor that an RMP merits consideration and discussion with the Agency. Both sponsor- and FDA-initiated approaches would be based on the benefits as well as the demonstrated risk profile of the drug product as characterized by the clinical development program, postmarketing surveillance, phase IV studies, or other risk information. Ideally, an RMP would be broached when the number or severity of a product's risks appears to undermine the magnitude of its benefits in an important segment of potential or actual users.

Benefits and risks can result in corresponding positive and negative effects on patient outcomes that may be cosmetic, symptomatic, curative, or affect mortality. Benefits and risks are numerous, varied, and measured in different units. No ready formula currently exists to determine when risks exceed benefits. As such, FDA anticipates that the decision to develop, submit, and implement an RMP will be made on a case-by-case basis. FDA anticipates that for most products that risk management planning will be

handled by the information contained in the PI. Submissions to FDA to revise the PI for adverse events would not automatically lead to an RMP being proposed.

#### **IV. WHAT INTERVENTIONS OR TOOLS ARE AVAILABLE FOR USE IN ACHIEVING RMP GOALS AND OBJECTIVES?**

A risk management intervention or tool is a process or system intended to enhance safe product use by reducing risk. There are a number of available tools, one or more of which could be used when designing and implementing a risk management program.

Professional product labeling is an important tool used to communicate risks and benefits. However, we plan to focus the draft guidance on risk management tools and strategies that a sponsor may implement above and beyond the package insert.

##### **A. How are tools related to RMP objectives and goals?**

RMP tools serve specific risk management program objectives. This relationship can be illustrated using the previous example of an RMP goal that no patient with condition A will be given product B. Examples of tools related to each of the sample objectives could include the following:

Objective: Physicians who are fully knowledgeable about withholding product B from patients with condition A.

Tools: Potential tools to achieve this objective could include:

1. Educating physicians with product labeling, detailing, CME, or other methods
2. Having physicians self-attest or be tested/certified that they possess the appropriate knowledge
3. Requiring documentation that condition A is not present prior to prescribing and dispensing
4. Limiting prescribing only to registered practitioners who meet certain requirements including being skilled in recognizing and monitoring condition A

Objective: Patients who are fully knowledgeable that condition A is contraindicated with product B and are able to help their prescriber know if they have condition A.

Tools: Potential tools to achieve this objective could include:

1. Patient education or self-assessment materials about condition A and its contraindication with product B
2. Office use of a checklist that actively solicits patient history or symptoms consistent with condition A

Objective: Pharmacists who confirm that a patient with a product B prescription does not have condition A.

Tools: Potential tools to achieve this objective could include:

1. Educational materials and training of pharmacists to ask patients if they have condition A
2. Having the pharmacist check for documentation from the prescriber that condition A is absent

3. Having the pharmacist check pharmacy records for evidence that condition A is likely to be present

The severity, reversibility, and rate of the risk being prevented will influence the extent and impact of risk management tools used to achieve specific objectives.

**B. What interventions or tools are being used in current RMPs?**

FDA is considering how best to describe the various types of tools that could be considered for use in a risk management program. Instead of specific tools being presented as part of a guidance document, FDA may maintain a more easily updated resource on its Website that describes tools that currently are in use.

In general, tools are employed to facilitate or constrain prescribing, dispensing, and/or use of a product to the most appropriate situations or patient populations. Tools used in current RMPs include but are not limited to the following:

1. Generalized education and outreach to health professionals and consumers/patients (beyond the package insert):
  - health care professional letters
  - training programs
  - CME and CE
  - public notices
  - patient package inserts
  - Medication Guides
2. Systems that guide the circumstances of individual prescribing, dispensing, and/or use:
  - patient agreements/ informed consent
  - certification programs for practitioners
  - enrollment of physicians, pharmacies, and/or patients in a safety program
  - limited supply or refills of product
  - specialized product packaging
  - specialized systems or records that attest to safety measures having been satisfied (e.g., stickers, physician attestation of capabilities)
3. Restricted access systems designed to enforce individual compliance with program elements
  - prescribing only by registered physicians
  - dispensing only by registered pharmacies or practitioners
  - dispensing only to patients with evidence or other documentation of safe use conditions (e.g., lab test results)
4. Marketing suspension with or without application withdrawal

Additional interventions or tools can be added to this list and FDA encourages the suggestion and development of other tools for inclusion.

### C. How can tools be best selected or developed?

We believe that the best tools would be those that are predicted to have a high likelihood of achieving their objective based on documented performance in other RMPs or in similar settings and populations. Relevant non-RMP evidence and experience may be found in health care quality initiatives, public health education and outreach, marketing, and other outcomes-based research.

Tools can be developed, selected, and negotiated based on their individual impact and/or for their impact when used in coordination with other tools. Some considerations in choosing the most effective tools include the following:

1. Input from key stakeholders such as physicians, pharmacists, patient groups, and third party payers on the feasibility of implementing and accepting the tool in usual healthcare practices, disease conditions, or lifestyles
2. Consistency with the existing tools that are familiar to and accepted by the targeted groups (e.g., physicians, pharmacists, patients)
3. Documented evidence of effectiveness<sup>3</sup> in achieving the specified objective (e.g., tools effectively used in pregnancy prevention)
4. Documented evidence of effectiveness in a related area that supports the rationale, design, or method of use (e.g., tools applied in modifying patient or health care professional behaviors in medical care settings)
5. Degree of variability, validity, and reproducibility in either method and/or results

Methods and considerations in developing evidence of effectiveness are discussed in the section V.

### D. How does the choice of tools for an RMP lead to its broad categorization?

For ready description and comparison of RMPs, FDA recommends they be broadly categorized into one of several “levels” to reflect how much the tools used in the RMP diverge from conventional prescribing, dispensing, and use. Increasing RMP levels would be related to increasing severity, frequency, or duration of the product’s risk(s). A proposed classification scheme for RMP levels follows:

Level 1: Package insert only

Level 2: Level 1 + education and outreach to health professionals and consumers/patients (examples in Section IV.B.1)

<sup>3</sup> Evidence may be based upon population studies, surveys, or qualitative methods such as focus groups.

Level 3: Level 2 + systems which guide the circumstances for practitioners and/or patients to prescribe, dispense, or receive a product (examples in Section IV.B.2)

Level 4: Access to product requires adherence to specific program elements from levels 2 and/or 3 (examples in Section IV.B.3)

## V. HOW AND WHEN CAN RISK MANAGEMENT PROGRAMS BE EVALUATED?

As discussed above, good risk management requires ongoing efforts to minimize a product's risks. As a result, evaluation is essential to monitor the effectiveness of risk management interventions. Through evaluation efforts, areas of improvement may be identified. Timely evaluation offers the opportunity to further minimize the product's risk and to improve the benefit/risk balance.

### A. Why is evaluation of risk management programs important?

Several studies have documented that previous risk communication and risk management interventions to reduce safety problems have been variably effective.<sup>4,5,6</sup> As such, FDA considers pretesting and evaluation of the effectiveness of an RMP to be very important. FDA is considering recommending that risk management tools be pretested prior to the implementation of the RMP and that a post-implementation evaluation plan be part of RMP submissions.

RMP evaluation is important for two reasons: (1) to predict the likelihood of whether an RMP will work before its full-scale implementation and (2) to determine whether or not an RMP, once implemented, is meeting its desired objectives. Stakeholder input, pretesting, pilot testing or drawing from previous similar product safety issues can increase the potential for good comprehension, acceptance, and feasibility of RMP components fitting into patient lifestyles and the everyday practices of physicians, pharmacists, and third party payers. After implementation of an RMP, periodic evaluations may lead to RMP alterations or redesign to increase or decrease the level of the RMP.

FDA recognizes that more than one evaluation method may be necessary to assess an RMP and that trade-offs of validity, accuracy, timeliness, representativeness, biases, societal impositions, and costs may occur. In the ideal situation, evaluation measurements (or metrics) will be of actual health outcomes. That is, the metric would

<sup>4</sup> Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess MJ. 2001. *Liver enzyme monitoring in patients treated with troglitazone*. JAMA 286(7):831-3.

<sup>5</sup> Smalley W, Shatin D, Wysowski D, Gurwitz J, Andrade S, Goodman, M, Chan, A, Platt, R, Schech, S, Ray, WA. 2000. *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action* JAMA 284(23):3036-3039.

<sup>6</sup> Weatherby LB, Nordstrom BL, Fife D, and Walker AM. 2002. *The impact of wording in "Dear Doctor" letters and in black box labels*. Clin Pharmacol Ther 72:735-742.

capture the outcome itself rather than some surrogate event or process. If process, rather than outcome, metrics are chosen, it will be important to review the scientific and other bases that link them to the ultimate outcome of interest. The ultimate goal of each evaluation is to ensure that efforts and costs involved in an RMP are expended on effective processes that achieve a positive benefit/risk balance.

RMP evaluation may be directed to assess both (1) the individual tools and (2) overall RMP effectiveness in achieving their prespecified objectives and goals.

## **B. What are the considerations for the overall approach to evaluation of risk management tools and programs?**

Ideally, an overall approach to RMP evaluation would:

1. Select well-defined, validated metrics. A sample outcome metric for reducing the occurrence of an adverse event could be analysis of the number or rate of hospitalizations for that event in an administrative data system. A sample process metric would be to measure how many patients prescribed a product get lab monitoring to reduce their risk of serious sequelae.
2. Use at least two different evaluation methods for key RMP goals or objectives. Preferably, the different evaluation methods would be both quantitative and representative to offset the biases that are intrinsic to any single evaluation process. For example, hospitalization data on an adverse event would not capture deaths that occurred out of the hospital; in such an instance, death certificate surveillance would offer complementary and more complete ascertainment of mortality risks. If it is not possible to implement two complementary representative methods, FDA suggests using other quantitative methods such as multiple site sampling or audits.
3. Use qualitative data collected from a large and diverse group of patients when quantitative data are either not available or not applicable to the evaluation measurement. Qualitative data such as focus group testing may be useful in assessing the effectiveness of education and comprehension about safety and risk information.
4. Consider using evaluation methods to assess if each RMP tool is performing as intended.

## **C. How can RMP effectiveness be measured?**

RMP objectives or goals can be evaluated for effectiveness using outcomes that measure whether targeted changes or levels of patient health outcomes were achieved (e.g., an acceptably low or reduced rate of an adverse event such as agranulocytosis.). If patient outcomes cannot be practically or accurately measured, closely related measures can be used such as the following:

1. Surrogates of health outcomes measures (e.g., co-prescribing of contraindicated medications)
2. Process measures that reflect desirable safety behaviors (e.g., performance of recommended laboratory monitoring)
3. Assessments of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks (e.g., provider, pharmacist, or patient surveys)

If risk communication or education is part of an RMP, pretesting materials in the target audience(s) is highly desirable to help ensure good comprehension and acceptance of the communication method and contents. A variety of testing methods such as focus groups, convenience samples, and surveys can be used as long as testing design ensures that participants are recruited in ways to minimize potential biases.

#### **D. What are the strengths and limitations of different evaluation methods?**

We do not recommend using spontaneous adverse event data as an outcome measure since reporting of adverse events varies due to many factors and represents an unknown and variable fraction of the adverse outcomes that are actually occurring. Continuing reports of adverse events may signal a persistent safety problem. A decrease in reporting does not constitute assurance that a safety issue has been resolved.

Some evaluation methods measure performance via administrative data systems that capture service or payment claims. Such systems often have limitations for evaluation purposes since the data are not collected with that purpose in mind. Generally, good evaluation design considers which individuals are covered and which are excluded from data systems and sampling methods. Excluded populations often experience higher risks by virtue of the same characteristics (such as poor health) that exclude them.

In addition to administrative claims data from various insurers, purchasing groups, or networks, surveys using various modes (in-person, mail, telephone, electronic) are another useful form of active surveillance. Reporting biases as well as sampling errors of such active surveillance systems merit consideration.

### **VI. WHAT ARE THE DESIRED ELEMENTS OF A RISK MANAGEMENT PROGRAM SUBMISSION?**

An RMP submission would describe (1) the background of the overall risk reduction goal(s) and rationale for the planned approach, (2) the targeted goals, objectives, and RMP level, (3) one or more proposed tools with a rationale and implementation plan for each, and (4) an evaluation plan for component tools and overall RMP objectives or goal(s) detailing the analyses that will be conducted and the plan for reporting the evaluation results to FDA.

**A. What information would the Background section contain?**

The Background section would characterize all the risks to be managed and the corresponding RMP goals for each. This section would address the rationale for why a risk management program is being considered and created. Sample questions to discuss would include:

1. What is the safety risk?
2. Who is at highest risk?
3. Are specific populations at risk (e.g., children, pregnant women, age, gender)?
4. Are the risks predictable?
5. Are the risks preventable?
6. Why is a program needed?

**B. What information would the Goals, Objectives, and Level section contain?**

This section would describe the goals and objectives of the RMP (as defined in section II.C) and their relationships to each other.

In addition, FDA recommends that this section describe and categorize the overall RMP into a level that reflects the severity, frequency, or duration of the product's risk(s) (see Section IV.D). The rationale for choosing that particular level over other levels would be addressed. Conditions or outcomes that would lead to revising an RMP to another level would be invited in this section, particularly when a product has serious or difficult-to-manage risks. For example, if risk education and communication were proposed for an RMP (a Level 2 program under the proposed categorization scheme) the sponsor would address the metric and the corresponding value of that metric that would prompt development of a Level 3 or higher RMP.

Where applicable and possible, the goals, objectives, and level section of the RMP would discuss potential unintended and untoward consequences of the RMP, particularly if there are therapeutic alternatives with similar risk profiles. In such a situation, an extensive RMP for one product in a therapeutic class may unintentionally encourage the use of equally risky products that do not have an effective RMP. Anticipating such situations will assist FDA in considering whether similar products should have an RMP. Yet another unintended consequence is that an RMP with component tools perceived to be burdensome by practitioners or patients could result in illicit access via the Internet or other outlets that circumvent the RMP.

**C. What information would the Tools section contain?**

The Tools section would:

1. Identify the risk management interventions or tool(s) that would be used and provide a rationale for choosing them to achieve the desired objective(s). This section could address how feasible it is to implement tools alone or in

combination based upon any assessments done of stakeholder support, abilities, or infrastructure.

2. Indicate how the tool(s) would be applied in the program (e.g., frequency, timing, and number of patients and/or health professionals in the targeted populations).
3. Identify all participants, stakeholders, and key influences (e.g., third party payers) who play a part in the application of the tool(s).
4. Describe how each tool fits into the overall RMP and its relation to the other tools.

In the Tools section, an implementation scheme would describe how and when each tool of the RMP is implemented and coordinated. Overall timelines and milestones would be specified.

#### **D. What information would the Evaluation Plan section contain?**

The Evaluation Plan section would address the success of tools in achieving overall RMP objectives and goals. As such, the evaluation plan would describe the nature and timing of data collection and analyses that would be used to assess the performance of tools vis-à-vis objectives and goals. Like a study protocol, data collection and analytical plans will prespecify the methods, validity, and precision of how the sponsor would measure effectiveness.

In the evaluation plan, sources of potential measurement error or bias would be discussed along with the methods to be used (e.g., sensitivity analyses) to account for them. Since RMP evaluations will often rely upon observational data, the analytical plan would appropriately address relevant issues such as the sensitivity and specificity of the measurements for the outcome, power and confidence intervals, as well as potential measurement errors and biases.

In an RMP submission, the evaluation plan would include an overall schedule for conducting analyses and submitting reports to FDA of individual tool performance, as well as achievement of objectives, and/or program goals. Process and outcome measures both merit inclusion. The tools being used and the outcome under consideration will influence the timing and frequency of analyses and reporting to FDA. FDA may propose that RMP progress reports and evaluations be included in periodic safety update reports (PSURs) or traditional periodic reports, with specific time points for re-evaluation of the overall RMP on a regular basis. To the maximum extent possible, a report of an RMP evaluation would contain the primary data, analyses, statistical estimation, and the sponsor's conclusions on how well the objectives or goals to reduce risk are being met and whether tools are performing as expected.